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Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

5/9/2022

RE: GRAS Notification of ***Bifidobacterium infantis*** **CBT BT1**
II964.1-CBI.1.4

To Whom It Concerns,

In accordance with 21 CFR, Part 170, Subpart E, we as the agent [REJIMUS, INC., 600 W. Santa Ana Blvd. Ste 1100, Santa Ana, CA 92701], respectfully provides notice of a claim that the addition of the microorganism ***Bifidobacterium infantis*** **CBT BT1** to the foods identified in this notice at the specified levels is exempt from the premarket approval requirement of the Federal Food, Drug and Cosmetic Act because the notifier [**Cell Biotech Co. Ltd.**, 50, Agibong-ro, 409 Beon-gil, Wolgot-myeon, Gimpo, Republic of Korea] has determined that the intended uses are generally recognized as safe (GRAS). The attached documents contain the specific information and data that address the safety of the substance for use in human food applications.

Respectfully,

Jim Lassiter, COO
REJIMUS, INC.
jim@rejimus.com

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PART 1 – SIGNED STATEMENTS AND CERTIFICATION

Cell Biotech Co. Ltd. submits this notification of a conclusion of GRAS through its agent, REJIMUS, INC. in accordance with 21 CFR §170.30.

Name and Address of Notifier and Agent

Agent:

Jim Lassiter
President/COO
REJIMUS, INC.
600 W. Santa Ana Blvd., Suite 1100
Santa Ana, CA 92701
Tel: +1 (949) 485-2112
www.rejimus.com

Notifier:

Cell Biotech Co. Ltd.
50, Agibong-ro, 409 Beon-gil
Wolgot-myeon, Gimpo
Republic of Korea
Tel: +82 31 987 6205

Name and Address of Manufacturer:

Cell Biotech Co. Ltd.
397 Aegibong-rol
Wolgot-myeon, Gimpo-si, Gyeonggi-do 415-872
Republic of Korea
Tel: +82 31 987 8107

Name of the GRAS Substance

Cell Biotech Co. Ltd. (herein referred to as CBI) has undertaken an independent safety evaluation of the substance in this notification:

***Bifidobacterium infantis* CBT BT1**

Intended Conditions of Use and Levels of Inclusion

The intended use of *Bifidobacterium infantis* CBT BT1 is a food ingredient for inclusion in dairy products where standards of identity do not preclude such use. The intended addition level to these foods is up to 1×10^{11} CFU per serving.

Bifidobacterium infantis CBT BT1 will not be added to meat and poultry products (including soups and soup mixes containing meat or poultry), and will not be included in foods that are marketed towards infants and young children, inclusive of infant formula. *Bifidobacterium infantis* CBT BT1 is not intended for addition to standardized foods unless it is permitted by the applicable standard of identity.

Basis for GRAS Conclusion

The statutory basis for conclusion of GRAS status is through scientific procedures in accordance with 21 CFR §170.30(a) and (b).

Premarket Approval Exemption

We have concluded that the intended use of *Bifidobacterium infantis* CBT BT1 is GRAS for its intended conditions of use as stated in this notification and, such use of *Bifidobacterium infantis* CBT BT1 is not subject to the premarket approval requirements of the *Federal Food, Drug, and Cosmetic Act.*

Availability of Information

The data and information that serve as the basis of GRAS conclusion are available for review and copying at reasonable times at the offices of the Agent.

Should FDA have any questions of additional requests for information regarding this notification, the Agent shall provide further clarification and/or information at:

Attn: Jim Lassiter
REJIMUS, INC.
600 W. Santa Ana Blvd., Suite 1100
Santa Ana, CA 92701
Email: jim@rejimus.com

Trade Secrets

The notification does not contain trade secrets and the data are not exempt from disclosure under the Freedom of Information Act, 5 U.S.C. Part 552.

Authorization for FDA to share information with FSIS

As Agent for the Notifier, we authorize FDA to send any information deemed necessary to FSIS. The notice does not contain trade secrets and the data are not exempt from disclosure under the *Freedom of Information Act*, 5 U.S.C. 552.

Certification

Cell Biotech Co. Ltd. has concluded that *Bifidobacterium infantis* CBT BT1 is generally recognized as safe for use in dairy products based on scientific procedures and supported by a history of use in accordance with 21 CFR Part 170, Subpart E. As their Agent, REJIMUS, INC. takes responsibility for all communications on this matter. To the best of our knowledge, this GRAS Notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to

us and pertinent to the evaluation of the safety and GRAS status of the use of *Bifidobacterium infantis* CBT BT1.

Respectfully submitted,

Jim Lassiter, COO
REJIMUS, INC.
jim@rejimus.com

PART 2 – IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

Common Name: *Bifidobacterium infantis* CBT BT1 (KCTC 11859BP)

Taxonomic Lineage (Accessed from the Integrated Taxonomic Information System [http:www.itis.gov]):

Kingdom: Bacteria
Subkingdom: Posibacteria
Phylum: Actinobacteria
Class: Actinobacteridae
Order: Bifidobacteriales
Family: Bifidobacteriaceae
Genus: *Bifidobacterium*
Species: *infantis*
Strain: CBT BT1

Previously designated *Bifidobacterium longum* subsp. *infantis, Bifidobacterium infantis* is a species of the genus *Bifidobacterium* and the class Actinobacteridae that can be isolated from human feces (Ventura et al. 2007). *Bifidobacterium* spp. are gram-positive, non-motile, non-spore forming, anaerobic rods with variable appearance (Candela et al. 2007). The gram staining morphology of *Bifidobacterium* can vary as long, slender rods, in clusters, pairs or even independently. *Bifidobacterium* are studied as other Lactic Acid Bacteria (LAB) since they are found predominantly in the gastric and intestinal mucosa. Nursing newborns may have a bifidobacteria population of more than 95% with this population decreasing as humans age (Toure et al. 2003). It is estimated that, on average, approximately 4% of the bacterial population of the adult human colon are bifidobacteria (Turroni et al. 2014).

Identification

The organism that is the subject of notified substance, originally isolated from human feces or fermented food is identified as *Bifidobacterium infantis* and has been uniquely characterized as a distinct strain known as CBT BT1 by means of genomic typing. The strain was deposited in the Korean Collection for Type Cultures (KCTC), accession number KCTC 11859BP.

Carbohydrate Utilization

Fermentative characteristics of *Bifidobacterium infantis* CBT BT1 were analyzed using API 50 CHL kit. Results are shown in Table 1.

Table 1. Fermentative Characteristics of *Bifidobacterium infantis* CBT BT1 obtained with an API 50 CHL Kit. (Cellbiotech R&D Center (2018))

No	Carbohydrates	Utilized	No	Carbohydrates	Utilized
0	Control	-	25	Esculine	-
1	Glycerol	-	26	Salicine	-
2	Erythritol	-	27	Cellobiose	-
3	D-Arabinose	-	28	Maltose	+
4	L-Arabinose	-	29	Lactose	+
5	Ribose	+	30	Melibiose	+
6	D-Xylose	-	31	Saccharose	+
7	L-Xylose	-	32	Trehalose	-
8	Adonitol	-	33	Inuline	-
9	β-Methyl-xyloside	-	34	Melezitose	-
10	Galactose	-	35	D-Raffinose	+
11	D-Glucose	+	36	Amidon	-
12	D-Fructose	-	37	Glycogene	-
13	D-Mannose	-	38	Xylitol	-
14	L-Sorbose	-	39	β-Gentiobiose	+
15	Rhamnose	-	40	D-Turanose	-
16	Dulcitol	-	41	D-Lyxose	-
17	Inositol	-	42	D-Tagatose	-
18	Mannitol	+	43	D-Fucose	-
19	Sorbitol	-	44	L-Fucose	-
20	α-Methyl-D-mannoside	-	45	D-Arabitol	-
21	α-Methyl-D-glucoside	-	46	L-Arabitol	-
22	N-Acetyl glucosamine	-	47	Gluconate	-
23	Amygdaline	+	48	2-Ceto-gluconate	-
24	Arbutine	-	49	5-Ceto-gluconate	-

Genomic Classification, Sequence, and Profile

The 16S rRNA gene sequence were aligned and compared with different *Bifidobacterium* strains: *B. infantis* (KCTC 11859BP), *B. infantis* (ATCC 15697), *B. longum* (ATCC 15707), *B. bifidum* (DSM 20456), *B. breve* (ATCC 15700), *B. lactis* (DSM 10140), and *B. catenulatum* (KCTC 3221). Percent identity and divergence were compared between *Bifidobacterium* species and strains in Table 2. As presented in Table 2, distinctive sequences of 16S rRNA genes were used to generate the phylogenic tree shown in Figure 1 (Cellbiotech R&D Center 2018).

Random Amplified Polymorphic DNA (RAPD) is a method used to obtain a molecular "fingerprint" from random DNA segments of genomic DNA that have been amplified using a single primer of an arbitrary nucleotide sequence. *Bifidobacterium infantis* CBT BT1 DNA was compared using RAPD with *Bifidobacterium infantis* ATCC 15697 strain. Both strains were amplified through PCR, ribotyping and pulsed-field gel electrophoresis (PFGE) in order to compare the RAPD patterns and genotypes between both species (Figure 2). Fragment yields presented difference between strains. DNA fragments were amplified with (GTG) primer (5' – GTGGTGGTGGTGGTG – 3') using genomic DNA as a template and analyzed in 0.8% agarose gel (Syngene, UK).

Pulse Field Gel Electrophoresis (PFGE) digests the genomic DNA with rare-cutting restriction enzymes. Separation of the macrofragments occurs via a continuously reorienting electric field. ***Bifidobacterium infantis* CBT BT1** (KCTC 11859BP) and *B. infantis* (ATCC 15697) strains were cultivated to OD_{600}=4 and treated with proteinase K and multiple restriction enzymes. DNA fragments from digestion were analyzed on agarose gel.

Table 2. Percent identity of *Bifidobacterium infantis* CBT BT1 with some closely related species and other closely related species based on 16S rRNA gene sequences. (Cellbiotech R&D Center 2018).

Percent Identity

Divergence

	1	2	3	4	5	6	7
1		99.5	99.2	93.9	96.4	90.3	93.2
2	0.2		98.9	93.4	96.8	90.8	93.0
3	0.8	0.9		93.4	95.8	90.6	93.7
4	4.5	4.6	5.1		92.9	89.3	94.1
5	2.4	2.3	3.1	4.6		91.4	93.1
6	7.2	6.9	7.0	7.6	6.3		90.9
7	5.2	5.2	5.0	4.9	5.1	6.7	

1 ***B. infantis* (KCTC 11859BP)**
2 *B. infantis* ATCC 15697
3 *B. longum* ATCC 15707
4 *B. bifidum* DSM 20456
5 *B. lactis* DSM 10140
6 *B. cantenulatum* KCTC 3221

Figure 1. Phylogenetic association between *Bifidobacterium infantis* CBT BT1 and closely related species based on 16S rRNA gene sequence. (Cellbiotech R&D Center 2018).

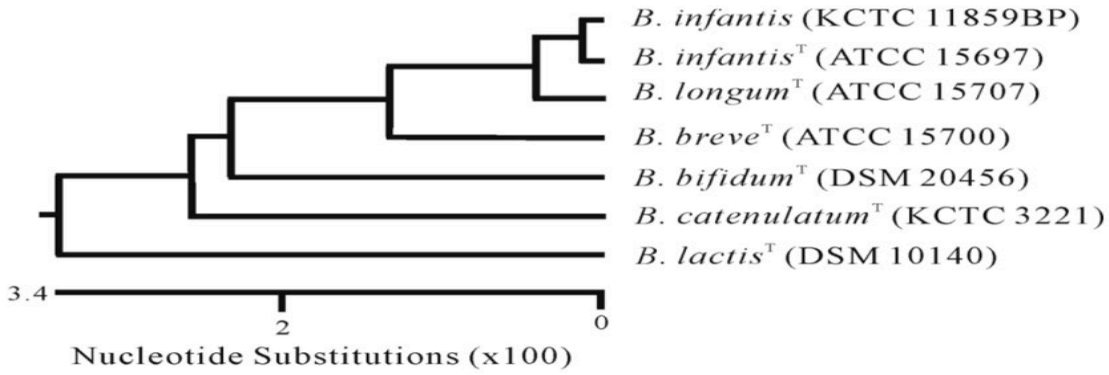
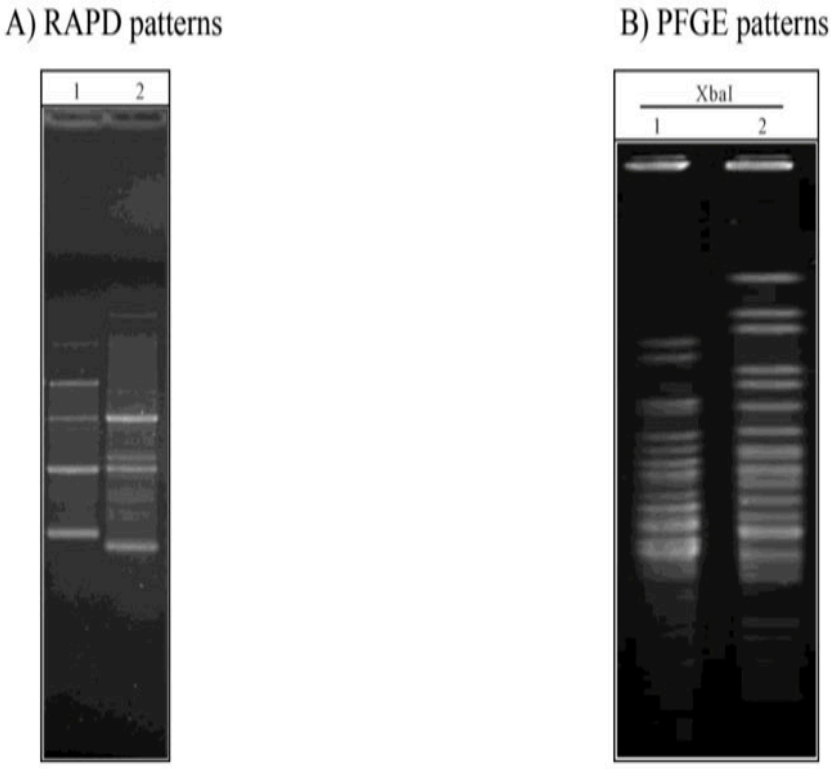


Figure 2. RAPD and PFGE results between *Bifidobacterium infantis* ATCC 15697- Lane 1 and *Bifidobacterium infantis* CBT BT1 (KCTC 11859BP).



Manufacturing

Components

All components employed in the manufacture of *Bifidobacterium infantis* CBT BT1 are suitably used for one or more effects described within FDA's Substances Added to Food Inventory as identified in Table 3.

Table 3. Identification of the ingredients used in the manufacturing process.

Fermentation Medium Ingredient	CAS No.	Reference
Dextrose Monohydrate	[77938-63-7]	21 CFR §168.111
Fructose	[57-48-7]	21 CFR §184.1866
Soy Peptone	[73049-73-7]	21 CFR §184.1553
Soy Protein Isolate	[977076-84-8]	21 CFR §184.1553
Yeast Extract Powder	[8013-01-1]	21 CFR §184.1983
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
Sodium acetate	[977127-84-6]	21 CFR §184.1721
Potassium Citrate	[6100-05-6]	21 CFR §184.1625
Calcium Chloride	[10043-52-4]	21 CFR §184.1193
Magnesium Sulfate	[10034-99-8]	21 CFR §184.1443
Manganese Sulfate	[15244-36-7]	21 CFR §182.5461
L-Cysteine Monohydrate	[7048-04-6]	21 CFR §184.1272
L-Ascorbic acid	[50-81-7]	21 CFR §182.8013
Monosodium L-Glutamate	[6106-04-3]	21 CFR §182.1
Polysorbate 80	[9005-65-6]	21 CFR §178.3400
Sodium Chloride	[7647-14-5]	21 CFR §182.1
Coating Ingredient	**CAS No.**	**Reference**
Trehalose	[6138-23-4]	FEMA No. 4600 (FEMA GRAS Publication No. 24)
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
Potassium Phosphate, Monobasic	[7778-7-0]	21 CFR §175.105
Xanthan Gum	[11138-66-2]	21 CFR §172.695
Cornstarch	[977050-21-3]	21 CFR §182.70 / 21 CFR §182.90
Sodium Carboxymethylcellulose	[9004-32-4]	21 CFR §182.1745

Fermentation Medium Ingredient	CAS No.	Reference
Sodium Chloride	[7647-14-5]	21 CFR §182.1
Excipient	**CAS No.**	**Reference**
Cornstarch	[977050-21-3]	21 CFR §182.70 / 21 CFR §182.90

Process Description and Flow Chart

The flowchart for the manufacturing process through packaging is shown at Figure 3.

Preparation of culture medium
All fermentation medium ingredients are blended together. The mixture is then sterilized with saturated steam.

Cultivation
Stock organism is prepared and tested for microbiological contaminants. The stock organism is then inoculated into the prepared medium where it is allowed to propagate. During fermentation, the process is monitored by testing for pH and for change in optical density approximately every two hours. Once the endpoint is reached, bacterial morphology is inspected by microscopy and the organisms are separated via filtration from the culture medium.

Preparation of coating materials
Coating ingredients are added to water, mixed, and sterilized with saturated steam.

Blending
The concentrated organisms, coating mixture, and cornstarch are blended together and then dispensed into trays for freezing.

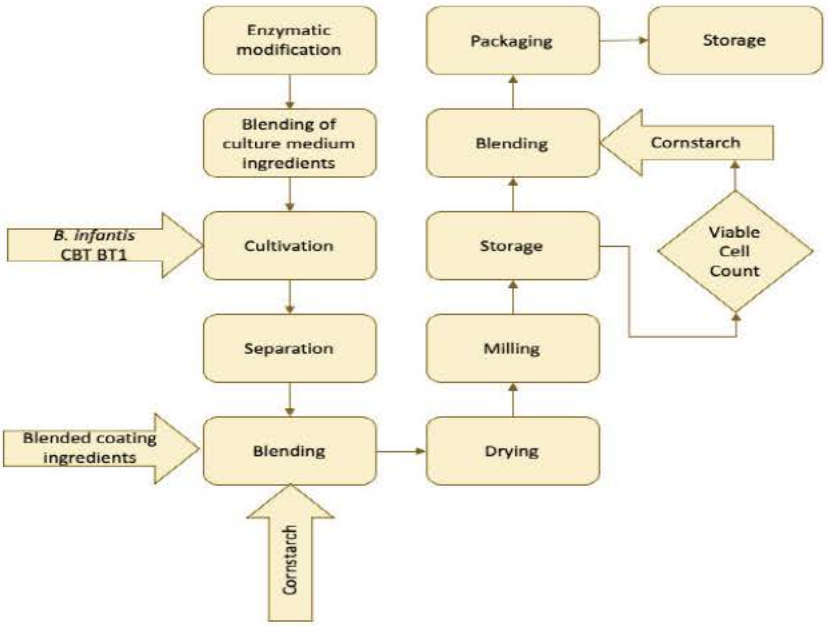
Drying
Trays containing the blended product are initially quick-frozen and then freeze dried.

Milling
Freeze-dried material is removed from the drying trays, milled, placed in polyethylene bags, passed through a metal detector, and stored as semi-finished product.

Standardization
The semi-finished product is tested for viable cell count and blended with a corresponding amount of cornstarch to ensure standardized potency.

Packaging
The standardized product is then packaged, passed through a metal detector again, sampled by QC for testing, and stored in a low -temperature warehouse.

Figure 3. Manufacturing process flow chart.



Specifications

Food grade specifications for *Bifidobacterium infantis* CBT BT1 have been established as shown in Table 4. Test results of three production batches are additionally presented in demonstration of the ability to consistently produce the notified substance in conformance with these specifications. Consistency of conformance to specifications is further evidenced by stability study results.

Table 4. *Bifidobacterium infantis* CBT BT1 food grade specifications and conforming test results.

Parameter	Limits	Method	Batch 08R	Batch 01R	Batch 44Q
Appearance	Light brown powder	Visual	Light brown powder	Light brown powder	Light brown powder
Viable Cell Count	$\geq 1.0 \times 10^{11}$ CFU/g	USP <2022> or equivalent	Conforms	Conforms	Conforms
Coliforms	Absent in 10g	USP <2023> or equivalent	Conforms	Conforms	Conforms

Stability Data

In order to determine the stability of *Bifidobacterium infantis* CBT BT1, the food ingredient was placed in a stability study by Cell Biotech Co. Ltd.

A 12-month stability study was conducted at 5 ± 3 °C using 3 different batches of *Bifidobacterium infantis* CBT BT1. At each time point, samples were analyzed in triplicate using 3 different analysts; the results of viable cell count assays are averaged and summarized in Table 5. Coliform testing was additionally performed by each analyst at all time points, the results of which are negative for all samples. Appearance test was performed by each analyst at all time points, the results of which were of a light brown powder.

Table 5. Viable cell count and percent survival rate of *Bifidobacterium infantis* CBT BT1 at 5 ± 3 °C.

Strain	Batch No.	Test	Time Point				
			Initial	3 Months	6 Months	9 Months	12 Months
***Bifidobacterium infantis* CBT BT1**	44Q	VCC (CFU/g)	2.64×10^{11}	2.39×10^{11}	2.05×10^{11}	1.84×10^{11}	1.69×10^{11}
		Survival Rate (%)	100.0	90.4	77.8	69.6	64.1
	01R	VCC (CFU/g)	3.35×10^{11}	3.04×10^{11}	2.72×10^{11}	2.33×10^{11}	2.04×10^{11}
		Survival Rate (%)	100.0	90.8	81.1	69.5	61.0
	08R	VCC (CFU/g)	4.48×10^{11}	4.19×10^{11}	3.49×10^{11}	3.15×10^{11}	2.85×10^{11}
		Survival Rate (%)	100.0	93.5	77.9	70.2	63.5
	Average Survival Rate (%)		100.0	91.6	78.9	69.8	62.9

Technical Effects

This substance will be used to provide as a dietary source of *Bifidobacterium infantis* CBT BT1 as a food ingredient to dairy products.

PART 3 – DIETARY EXPOSURE

Intended Use and All Sources in the Diet

The intended use of *Bifidobacterium infantis* CBT BT1 is as a food ingredient for inclusion in dairy products to provide at least 1×10^{11} CFU per serving.

The consensus of an international scientific expert panel categorized live microorganisms for human use as defined in Table 6. The panel suggested a minimum level of 1×10^{9} CFU of LAB per serving to be the minimum criteria in support a claim of "contains live and active cultures." (Hill 2014)

Table 6. Categories of live microorganisms for human use (Hill et al. 2014).

Description	Claim	Criteria*	Minimum level of evidence required to make claim	Comments
Not probiotic				
Live or active cultures	"Contains live and active cultures"	Any food fermentation microbe(s) Proof of viability at a minimum level reflective of typical levels seen in fermented foods, suggested to be 1×10^{9} CFU per serving[73]	No product-specific efficacy studies needed	The terms 'live' or 'active' do not imply probiotic activity Fermented foods containing live cultures might also qualify as a 'probiotic' if they meet the criteria for that category (e.g. evidence that yogurt can improve lactose digestion in lactose maldigesters would qualify it as a 'probiotic'[74,75])
Probiotic				
Probiotic in food or supplement without health claim	"Contains probiotics"	A member(s) of a safe[76,77] species, which is supported by sufficient evidence of a general beneficial effect in humans OR a safe microbe(s) with a property (e.g. a structure, activity or end product) for which there is sufficient evidence for a general beneficial effect in humans Proof of viability at the appropriate level used in supporting human studies[73]	Well-conducted human studies (e.g. these could involve RCT(s), observational studies, systematic reviews or meta-analyses supporting the observed general beneficial effect for the taxonomical category concerned) The evidence does not have to be generated for the specific strain included in the product	Extrapolation of evidence must be based on reasonable expectations that the strain(s) incorporated in the product would have similar general beneficial effects in humans This evidence could be based on taxonomical or functional comparisons
Probiotic in food or supplement with a specific health claim	Specific health claim, such as "helps to reinforce the body's natural defences in children" or "helps reduce the risk of antibiotic-associated diarrhoea"	Defined probiotic strain(s) Proof of delivery of viable strain(s) at efficacious dose at end of shelf-life[73]	Convincing evidence needed for specific strain(s) or strain combination in the specified health indication Such evidence includes well-conducted studies in humans, including: positive meta-analyses on specific strain(s) or strain combinations, as per principles outlined by Cochrane,[78] PASSCLAIM,[79] or GRADE;[80] well-conducted RCT(s) OR strong evidence from large observational studies[81]	Well-designed observational studies are useful to detect the effect of foods on health in 'real life', that is, outside the controlled environment of an RCT (e.g. data on health benefits by dietary fibre are mostly observational) Sample sizes must be large enough to manage confounding factors
Probiotic drug	Specific indication for treatment or prevention of disease, such as "useful for the prevention of relapse of ulcerative colitis"	A defined strain(s) of live microbe Proof of delivery of viable probiotic at efficacious dose at end of shelf-life Risk–benefit assessment justifies use	Appropriate trials to meet regulatory standards for drugs	What constitutes a drug claim varies among countries

*Unless otherwise indicated, all criteria indicated must be met. Abbreviations: CFU, colony forming unit; GRADE, Grades of Recommendation Assessment, Development and Evaluation; PASSCLAIM, Process for the Assessment of Scientific Support for Claims on Food; RCT, randomized controlled trial.

Consumption Data

Based on the food consumption data reported in the most recent National Health and Nutrition Examination Survey (NHANES 2017-2018) dataset compiled by the U.S. Department of Health and Human Services, National Center for Health Statistics, and the Nutrition Coordinating Center, the EDIs of dairy products were determined by several age groups.

The intended use of at least 1.0 x 10^{11} CFU per serving in dairy products would result in intakes in all users of 8.94 x 10^{10} CFU and 1.85 x 10^{11} CFU per person per day in the mean and 90th percentile, respectively (Table 7). A maximum exposure would occur in male adults with a 90th percentile EDI of 2.05 x 10^{11} per person per day.

Table 7. EDIs of *Bifidobacterium infantis* CBT BT1 from proposed uses in dairy products across all users based on 2017-2018 NHANES.

Group	% (n)	Dairy intake g/day		Dairy, serving/day		*Bifidobacterium infantis* CBT BT1, cfu/day	
		Mean	90th percentile	Mean	90th percentile	Mean	90th percentile
Children, 3-11	74.04 (739)	360.44	456.85	0.97	1.87	9.74×10^{10}	1.87×10^{11}
Females, 12-19	42.44 (191)	186.02	362.90	0.76	1.49	7.62×10^{10}	1.49×10^{11}
Males, 12-19	54.73 (243)	265.10	477.28	1.09	1.96	1.09×10^{11}	1.96×10^{11}
Females, 20 and up	38.21(826)	179.05	360.87	0.73	1.48	7.34×10^{10}	1.48×10^{11}
Males, 20 and up	44.06(871)	222.93	499.63	0.91	2.05	9.13×10^{10}	2.05×10^{11}
All users	47.61(3161)	218.16	452.44	0.89	1.85	8.94×10^{10}	1.85×10^{11}

Assuming all servings of the intended dairy products consumed contain *Bifidobacterium infantis* CBT BT1, the suggested three daily servings would result in a cumulative exposure of 2.68 × 10^{11} CFU per day ($8.94\times10^{10}\times3$). The estimated 90th percentile of consumers of dairy products at this level of recommended consumption adjusted for the findings of the per capita data would potentially be exposed to up to 5.55 × 10^{11} CFU per day *Bifidobacterium infantis* CBT BT1. The LD_{50} identified is the uppermost safety point that has been studied to date. The study presented by CBI R&D Center (2018) demonstrated that > 10^{11} CFU/kg was still safe for the rats at that dosage. In point of fact, no true LD_{50} nor NOAEL has ever been determined for this organism. This is due to the fact that an amount of organism greater than this cannot feasibly be administered to the rats.

The LD_{50} of greater than 10^{11} CFU/kg from the animal studies from the Cell Biotech R&D Center corresponds to the human equivalent dose of 9.6 × 10^{11} CFU in a 60 kg human (using the animal-specific body surface area-based conversion factor presented in the Center for Drug Evaluation and Research's Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers 2005). Therefore, even if the general population consumers of dairy products were to meet these guidelines, the recommended levels of the cumulative exposure of 2.68 × 10^{11} CFU

per day and the cumulative exposure at an estimated 90th percentile of 5.55 × 10^{11} CFU per day is less than the LD_{50} levels of greater than 10^{11} CFU/kg (or 9.6 × 10^{11}) of *Bifidobacterium infantis* CBT BT1**.**

Substances Expected to Be Formed in Food

Under the intended conditions of use, there are no substances expected to be formed in the foods in which *Bifidobacterium infantis* CBT BT1 is included. The metabolic by-products from *Bifidobacterium infantis* CBT BT1 do not go beyond the expected fermentation products from any of the other LAB microorganisms. These include lactic acid, carbon dioxide and the ATP necessary for the cell. *Bifidobacterium infantis* CBT BT1 is not known to secrete any exotoxins or any other substances that are classified as harmful to humans. Additionally, the number of viable organisms will decline during a product's shelf life to further minimize the exposure to any of the metabolic by-products.

Substances Naturally Present or Due to Manufacturing

Any remaining ingredients used to produce the fermentation media should have little to no presence in the overall finished output and therefore, the EDIs for these ingredients were not determined or calculated.

The coating ingredients and excipients used in the manufacturing process are listed in FDA's Substances Added to Food Inventory for various uses:

- Trehalose is listed as a flavoring agent or adjuvant.
- Potassium phosphate, dibasic is listed as an emulsifier or emulsifier salt, nutrient supplement, pH control agent, sequestrant, or stabilizer or thickener.
- Potassium phosphate, monobasic is listed as malting or fermenting aid, nutrient supplement, pH control agent, or stabilizer or thickener.
- Xanthan gum is listed as an anticaking agent or free-flow agent, color or coloring adjunct, drying agent, emulsifier or emulsifier salt, formulation aid, processing aid, solvent or vehicle, stabilizer or thickener, surface-finishing agent, or texturizer.
- Cornstarch is listed as an anticaking agent or free-flow agent, drying agent, flavoring agent or adjuvant, formulation aid, humectant, non-nutritive sweetener, nutritive sweetener, solvent or vehicle, stabilizer or thickener, or texturizer.
- Sodium carboxymethylcellulose is listed as an anticaking agent or free-flow agent, drying agent, emulsifier or emulsifier salt, formulation aid, processing aid, humectant, stabilizer or thickener, or texturizer.
- Sodium chloride is listed as an anticaking agent or free-flow agent, antimicrobial agent, color or coloring adjunct, emulsifier or emulsifier salt, firming agent, flavoring agent or adjuvant, formulation aid, nutrient supplement, solvent or vehicle, stabilizer or thickener.

PART 4 – SELF-LIMITING LEVELS OF USE

There is no recognized self-limiting level of use for this organism. Issues of palatability of the substance are not present at the levels of inclusion identified.

PART 5 – EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

As the conclusion of general recognition of safety is through scientific procedures, this Part is not applicable. Information about the current international marketplace availability of products containing *Bifidobacterium infantis* CBT BT1 as an ingredient is discussed as part of the scientific procedures upon which the general recognition of safety is based. Nevertheless, the historical use of foods with *Bifidobacterium infantis* is discussed in Part 6.

PART 6 – NARRATIVE

Introduction

Fermented foods have a long history of consumption in the human population, with some of the earliest records of such in Southeast Asia and Africa (Nout 1992). Prevalence of fermented foods is much higher in some parts of the world outside the U.S., such as in Sudan where it seems the majority of foods are prepared and preserved by fermentation (Dirar 1992).

Used as an inexpensive means throughout the world, lactic acid-producing bacteria (LAB) are one major group of microorganisms used to process milk, meat, and various plant material like vegetables, cereals, and legumes into fermented foods that undergo flavor and nutritive profile changes from their original forms as well as gain the benefit of improved stability (Steinkraus 1992). By preventing the formation of pathogenic and spoilage organisms, fermented foods have an increased shelf life and decreased potential for causing food poisoning (Hesseltine 1981).

In the United States, LAB in general are permitted for use in several standardized foods. A variety of cheeses, whose requirements are found within 21 CFR Part 133—Cheeses and Related Cheese Products, include the use of these and other types of bacterial cultures. LAB are also used in the production of Sour Cream [§131.160], are optional ingredients for use in Bread, Rolls, and Buns [§136.110(c)(10)], and may be used as characterizing microbial organisms or as microbial cultures to produce aroma and flavor in the production of Acidified Milk [§131.111] and Cultured Milk [§131.112].

History of GRAS Notices

There is a history of successfully notified GRAS substances intended for inclusion in foods dating back to 2002 (GRAS No. 49).

GRAS notices of food ingredient substances containing the same species as *Bifidobacterium infantis* CBT BT1 to which FDA has no questions are presented below in Table 8. These GRAS notices reference and address a large body of established scientific procedures evidencing the safe and common use of various strains of *Bifidobacterium infantis* and its subspecies. GRAS notices of *Bifidobacterium* organisms of species other than *infantis* which FDA has no questions are presented below in Table 9.

Table 7. GRAS notices containing *Bifidobacterium infantis* receiving reply from FDA that it had no questions (GRAS Notices Inventory Database).

GRAS No.	Date of Closure	Substance
758	20-Aug-2018	*Lactobacillus helveticus* strain R0052, *Bifidobacterium longum* subsp. *infantis* strain R0033, and *Bifidobacterium bifidum* strain R0071
268	08-Jul-2009	*Bifidobacterium longum* strain BB536

Table 9. GRAS notices of *Bifidobacterium* organisms of species other than *infantis* receiving reply from FDA of no questions (GRAS Notices Inventory Database)

GRAS No.	Date of Closure	Substance
877	26-Dec-2019	*Bifidobacterium longum* BB536
872	9-Dec-2019	*Bifidobacterium animalis* subsp. *lactis* UABla-12
856	09-Dec-2019	*Bifidobacterium animalis* subsp. *lactis* strain BB012
855	05-Feb-2020	*Bifidobacterium animalis* subsp. *lactis* strain R0421
814	25-Jun-2019	*Bifidobacterium bifidum* BGN4
813	21-Jun-2019	*Bifidobacterium bifidum* BORI
455	30-Sep-2013	*Bifidobacterium breve* M-16V
454	27-Sep-2013	*Bifidobacterium breve* M-16V
453	27-Sep-2013	*Bifidobacterium breve* M-16V
445	10-Apr-2013	*Bifidobacterium animalis* subsp. *lactis* strains HN019, Bi-07, BI-04 and B420
377	29-Sep-2011	*Bifidobacterium animalis* subsp. *lactis* strain Bf-6

Approved Use

The status of *Bifidobacterium infantis* in Canada involves the accepted use of the microorganism in food products. Specific claims may be made about these products when the level of use is a minimum of 1×10^9 CFU per serving.

In a December 12th, 2019 update to their Qualified Presumption of Safety list, the European Food Safety Authority confirmed *Bifidobacterium* spp. (including *Bifidobacterium longum*) presence in an inventory of recommended biological agents intentionally added to food or feed based on review of latest applicable literature. *Bifidobacterium infantis* is a subspecies of *Bifidobacterium longum.*

Antibiotic Resistance

Determination of the minimal inhibitory concentration (MIC) of select antibiotics [ampicillin (AMP), gentamycin (GEN), kanamycin (KAN), streptomycin (STM), erythromycin (ERM), clindamycin (CLM), tetracycline (TET), and chloramphenicol (CP)] was performed in accordance with ISO 10932:2010 using *Bifidobacterium infantis* CBT BT1 as the test strain. Observed MIC values for *Bifidobacterium infantis* CBT BT1 were determined to be lower than the cut-off values prescribed by 2012 Guidance on the assessment of bacterial susceptibility to antimicrobials of human and veterinary importance published by the European Food Safety Authority (EFSA), as shown in Table 10 and therefore the strain is susceptible to AMP, GEN, KAN, STM, ERM, CLM, TET, and CP. Most *Bifidobacterium* species are reported to be resistant to aminoglycosides, because of the lack of a cytochrome-mediated drug transport system and the particular resistance to kanamycin is well known and testing for such in *Bifidobacterium infantis* is not required by EFSA guidance (EFSA 2012).

Table 10. Antibiotic susceptibility of *Bifidobacterium infantis* CBT BT1 (Cellbiotech R&D Center (2018)).

Strain	**Minimum Inhibitory Concentrations (μg/mL) of Antibiotics**								
	AMP	VAN	GEN	KAN	STM	ERM	CLM	TET	CP
***B. infantis* CBT BT1**	<2	<0.5	<8	<128	<16	<0.5	<0.06	<8	<2
EFSA Cut-off Value	2	2	64	NR	128	1	1	8	4

Current Marketplace Availability of *Bifidobacterium infantis* CBT BT1

While the conclusion of general recognition of safety (GRAS) is based upon scientific procedures, there is a history of use of *Bifidobacterium infantis* CBT BT1 in foreign countries and in multiple food products.

In vitro Toxicity Studies

Hemolysis Assay

The Cell Biotech R&D Center tested *Bifidobacterium infantis* CBT BT1 for its hemolytic activity by inoculating microorganism in MRS agar supplemented with 5% horse blood and incubated under anaerobic conditions. The test showed no hemolytic activity.

Animal Studies

The pathogenicity and acute toxicity of ***Bifidobacterium infantis* CBT BT1** were investigated using male and female Sprague-Dawley rats (5 of each sex in each group). The animals were intragastrically

administered either 0.85% saline solution or 1×10^{11} CFU/kg ***Bifidobacterium infantis*** **CBT BT1** and observed for the ensuing 14 days. The net body weight gain, gross pathological findings, feed and water consumption, organ weight, and body temperature were monitored and recorded for two (2) weeks.

This investigation revealed no mortalities or obvious adverse clinical signs in rats administered with the live bacterial cells at the investigated dose level as shown on Table 11. In addition, results indicate no significant differences in net body weight gain (Figure 4), gross pathological findings (Table 12), feed and water consumption (Figure 5), organ weight (Table 13), and body temperature (Table 14) among the different treatment groups and between the treated and control rats.

Table 11. Mortality of male and female rats orally administered with 1×10^{11} CFU/kg *Bifidobacterium infantis* CBT BT1 (Cellbiotech R&D Center (2018))

Sex	Group	Days After Administration														Final Mortality (%)	LD_{50}
		1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Male	CBT BT1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	> 1 x 10^{11} CFU/kg
	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Female	CBT BT1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	> 1 x 10^{11} CFU/kg
	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Figure 4. Body weight curves for male and female rats given 10^{11} CFU/kg *Bifidobacterium infantis* CBT BT1 and control for 14 days. Values are mean ± SE. (Cellbiotech R&D Center (2018))

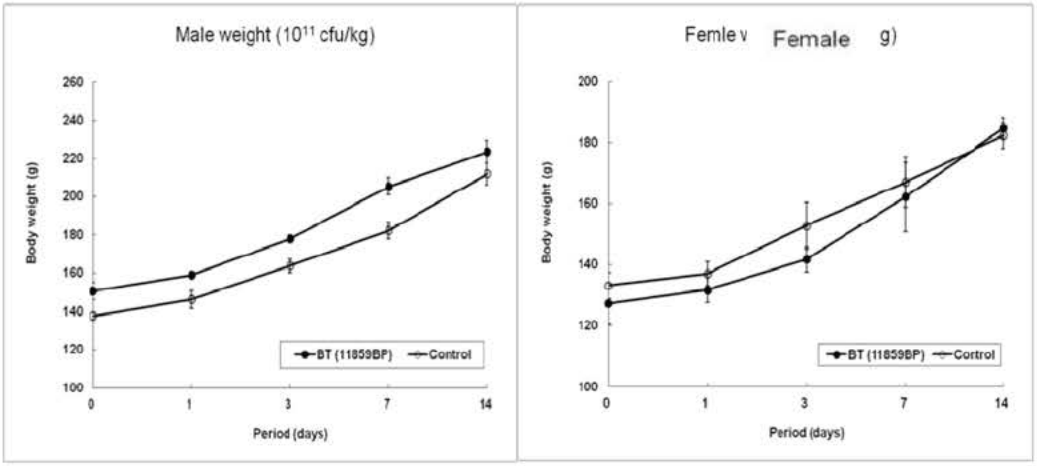


Table 12. Clinical findings of male and female rats orally administered with 10^{11} CFU/kg *Bifidobacterium infantis* CBT BT1 (Cellbiotech R&D Center (2018))

Sex	LAB Strain	Clinical Signs	Hours after treatment				Days after treatment				
			1	2	5	6	1	3	5	7	14
Male	CBT BT1	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
	Control	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
Female	CBT BT1	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
	Control	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5

NAD: No abnormality detected

Figure 5. Food and water consumption of male and female rats given 10^{11} CFU/kg *Bifidobacterium infantis* CBT BT1 and control for 14 days. (Cellbiotech R&D Center (2018))

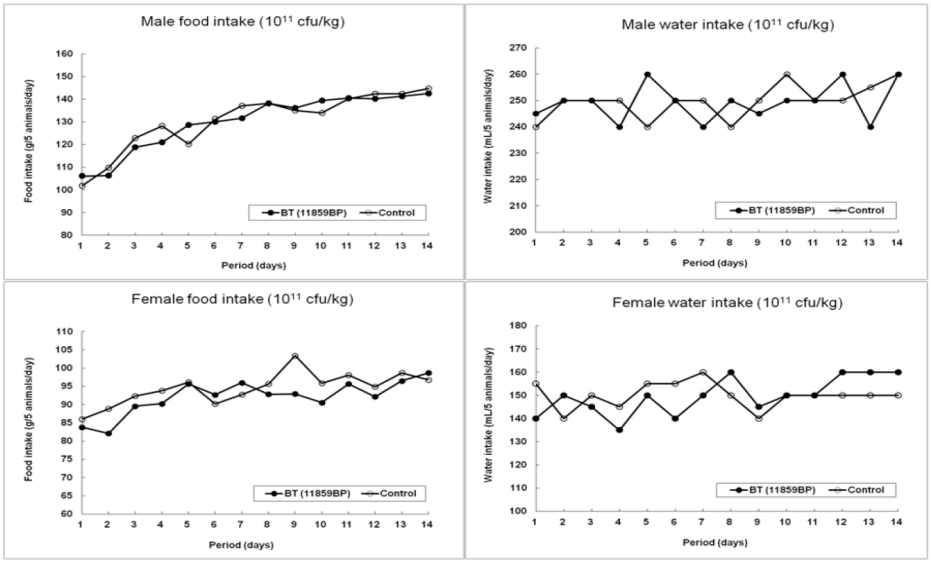


Table 13. Absolute organ weights (g) of male and female orally administered with 10^{11} CFU/kg *Bifidobacterium infantis* CBT BT1 (Cellbiotech R&D Center (2018))

Sex	Parameters	Lab	CBT BT1	Control
		No. of Animals	5	5
Male	Body weight (g)		223.56 ± 5.84	211.90 ± 5.66
	Liver (g)		7.45 ± 0.52	7.20 ± 0.70
	Spleen (g)		0.87 ± 0.05	0.79 ± 0.05
	Kidney (g)	Right	0.88 ± 0.04	0.81 ± 0.09
		Left	0.45 ± 0.07	0.30 ± 0.06
Female	Body weight (g)		184.67 ± 3.65	182.32 ± 4.33
	Liver (g)		5.52 ± 0.92	5.32 ± 0.53
	Spleen (g)		0.62 ± 0.07	0.63 ± 0.05
	Kidney (g)	Right	0.63 ± 0.11	0.66 ± 0.05
		Left	0.37 ± 0.06	0.32 ± 0.04

Table 14. Body temperature changes in male and female orally treated with 10^{11} CFU/kg *Bifidobacterium infantis* CBT BT1 (Cellbiotech R&D Center (2018))

Day	No.	Male body temperature		Female body temperature	
		CBT BT1 (˚C)	Control (˚C)	CBT BT1 (˚C)	Control (˚C)
Pre-treatment	Ave	35.52	34.40	32.20	35.16
	SEM	0.96	0.24	0.81	0.70
Day 1	Ave	35.18	34.70	34.64	35.08
	SEM	0.83	0.92	0.43	0.66
Day 2	Ave	35.08	34.90	35.42	35.12
	SEM	0.46	0.56	0.39	0.83
Day 3	Ave	35.40	35.10	35.20	35.36
	SEM	0.62	0.69	0.25	0.32

Day 4	Ave	35.82	34.10	35.12	35.30
	SEM	0.39	0.60	0.13	0.30

Human Studies

Study 1

Del Giudice et al. (2017) conducted a placebo-controlled, double-blind, randomized clinical trial that investigated the effects of *Bifidobacterium* on allergic symptoms due to pollen allergy. Forty children were treated with either bacterial (oral supplementation containing 1×10^9 CFU of *Bifidobacterium infantis* with *Bifidobacterium longum* and *Bifidobacterium breve*) or placebo daily for 8 weeks. The treatment was well tolerated, significantly reduced nasal symptoms, and improved quality of life. No clinically relevant side effects were noted in either group.

Study 2

Groeger et al. (2013) studied the effects of *Bifidobacterium infantis* on inflammatory biomarker and plasma cytokine levels in 96 patients suffering from ulcerative colitis, chronic fatigue syndrome or psoriasis in three separate randomized, double-blind, placebo-controlled interventions performed over 6-8 weeks. Effects of treatment on immunological biomarkers in 22 healthy subjects were also assessed. Each participant received either 1×10^{10} CFU viable *Bifidobacterium infantis* cells or placebo daily. The results showed an overall reduction in systemic pro-inflammatory biomarkers in all three conditions as well as in the healthy subjects administered the microbial treatment. No adverse events were reported.

Study 3

Smilowitz et al. (2017) conducted a Phase I clinical trial with 80 mother-breast fed infants to determine safety and tolerability of supplementing breast milk with *Bifidobacterium infantis*. Infants were fed breastmilk supplemented with $1.8 - 10^8 – 2.8 \times 10^8$ CFU *Bifidobacterium infantis* daily or breast milk alone for 21 days. The *Bifidobacterium infantis* treated group passed fewer, better formed stools than the control group. There were no differences in the safety and tolerability endpoints between supplemented and non-supplemented infants.

Study 4

Hoyos (1999) *Bifidobacterium infantis* and *Lactobacillus acidophilus* (2.5×10^8 viable cells each) were given as daily doses, until discharge from the hospital, to all 1237 newborns admitted to an intensive care unit over the course of a year. Information from 1282 infants hospitalized during the previous year were used as the study control. The incidence of necrotizing enterocolitis in patients treated with specific microorganisms was reduced to one third compared to the control group. No complications were attributed to the microbial therapy treatment (Hoyos 1999).

Study 5

Whorwell et al. (2006) conducted a randomized, double-blind, placebo-controlled, multicenter, dose-ranging study with 362 female patients suffering from irritable bowel syndrome to confirm the efficacy of treatment with an encapsulated *Bifidobacterium infantis* strain and to determine the optimal dosage. Subjects received once daily treatment with a capsule containing either 1×10^6, 1×10^8, or 1×10^{10} CFU of *B. infantis*, or placebo, for 4 weeks. The median microbial dose was significantly superior to placebo and other treatments in symptom reduction (the high dose suffered from formulation coagulation problems). The authors reported that the treatment was remarkably well tolerated.

Study 6

Bazanella et al. (2017) conducted a randomized, double-blind, placebo-controlled study to determine the first year of life effects of a formula containing *Bifidobacterium* spp. on the healthy infant intestinal microbiome. The treatment group consisted of 48 newborn infants provided with a supplemented formula containing a total of 1×10^8 CFU/g of *Bifidobacterium*, including *Bifidobacterium infantis* CBT BT1 with 3 other *Bifidobacterium* in equal amounts, from birth to 12 months. The supplemented formula was shown to impact the early stage of microbiome development with no detectable long-term consequences.

Study 7

Escribano et al. (2017) conducted a multicenter, double-blind, randomized, placebo-controlled clinical trial. Infants were fed an infant formula supplemented with 1×10^7 CFU/g of *Bifidobacterium infantis* over twelve weeks. Evaluation of the 73 treated infants and 78 controls that completed the follow up led researchers to conclude that the supplemented infant formula was well tolerated, safe, and may reduce the occurrence of diarrhea while lowering the prevalence of constipation.

Study 8

Hod et al. (2017 and 2018) investigated the effects of a microorganism mixture in 107 adult women diagnosed with diarrhea-dominant-IBS (IBS-D). The study was designed as a randomized double-blind, placebo-controlled, parallel-group trial with a 2-week run-in period prior to treatment and a treatment period for 8 weeks. Those subjects in the BIO-25 group were given a BIO-25 capsule containing 2.5×10^{10} CFU microorganism mixture of 11 bacteria twice daily that contained 2×10^9 CFU *Bifidobacterium infantis* CBT BT1. A total of 54 subjects were used in the BIO-25 group and 53 subjects were used in the placebo group. Nine subjects in the placebo group and five subjects in the BIO-25 group did not complete the study. No serious adverse events were reported in either group. The studies concluded improved symptoms in women with IBS-D but did not demonstrate superiority of symptoms and microbial diversity of the microorganism mixture over the placebo group.

Conclusion

The scientific data, information, methods, and principles described in this notification provide the basis for conclusion that *Bifidobacterium infantis* CBT BT1 is generally recognized among qualified experts to be safe for inclusion in the food types described in the amounts noted. The historic safe use of *Bifidobacterium infantis* in the food supply along with the evaluation of the consumption data serve as the foundation on which the safety of this uniquely identified strain is established.

Inclusion of *Bifidobacterium infantis* and other lactic acid-producing bacteria is identified and sometimes mandated in FDA regulations surrounding standards of identity for select food types. FDA has also responded with no questions to numerous GRAS notices submitted for other strains of *Bifidobacterium infantis*, other species of *Bifidobacterium*, as well as members of other genera of lactic acid-producing bacteria, intended for inclusion as food ingredients. The applicable GRAS notices, referenced in Table 8 and Table 9 within Part 6 of this notice, incorporate myriad studies demonstrating the safety of ingestion of substances closely related to *Bifidobacterium infantis* CBT BT1**.**

Bifidobacterium infantis CBT BT1 is well characterized genetically, taxonomically known as an organism lacking potential for harm, and supported by analyses conducted by Cell Biotech R&D Center (2018) in demonstration of its safety and elucidation of its genotypic and phenotypic traits. The substance's potential for pathogenicity and acute toxicity tested negative. *Bifidobacterium infantis* CBT BT1's potential for antibiotic resistance was tested in accordance with EFSA guidelines where *Bifidobacterium* strains are intrinsically resistant to kanamycin.

Additional efficacy studies in humans and animals have been performed without the occurrence of observation of adverse events. An LD_{50} of greater than 10^{11} CFU/kg was established in rats which corresponds to a human equivalent amount of 9.6×10^{11} CFU in a 60kg human (using the animal-specific body surface area-based conversion factor presented in the Center for Drug Evaluation and Research's Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [2005]). The estimated level of cumulative daily intake of *Bifidobacterium infantis* CBT BT1 at the 90th percentile of high-level consumers of products of the intended inclusion food is 5.55×10^{11} CFU per day of *Bifidobacterium infantis* CBT BT1. The 90th percentile for actual consumption of 5.55×10^{11} CFU/day is below the maximum safe starting dose of 9.6×10^{11} CFU/serving.

All data and information pertaining to the studies performed on the material, in-house documentation, and additional information were made available to the Expert Panel, and their findings reflect review of the totality of the information used in the preparation of this notice as shown on the Expert Panel Endorsement pages.

PART 7 – SUPPORTING DATA AND INFORMATION

Generally Unavailable

Cellbiotech R&D Center (2018) Identification. Molecular Typing and Safety Assessment of *Bifidobacterium infantis* CBT BT1 (KCTC 11859BP).

Generally Available

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Cell Biotech Co. Ltd. *Bifidobacterium infantis* CBT BT1

February 25, 2021

Cell Biotech Co. Ltd. intends to market ***Bifidobacterium infantis* CBT BT1** as an ingredient in dairy products. ***Bifidobacterium infantis* CBT BT1** is produced by growth of a certified source strain of the organism in an appropriate medium. The strain is verified prior to inoculation of the medium. The resultant microorganism is freeze-dried for use in dairy products.

The use of this microorganism in the production of food products is historic. The application of the specific strain ***Bifidobacterium infantis* CBT BT1** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Cell Biotech Co. Ltd., a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Bifidobacterium infantis* CBT BT1** as an ingredient in dairy products is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Mary C. Mulry, Ph.D. (Foodwise), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. ***Bifidobacterium infantis* CBT BT1**, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products that include Cell Biotech Co. Ltd. ***Bifidobacterium infantis* CBT BT1** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good

Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on a combination of historic use of the microorganism in food products with support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY STEVEN DENTALI, PH.D.

I, Steven Dentali, hereby affirm that ***Bifidobacterium infantis* CBT BT1** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature:__  Date:17 March 2021

Steven Dentali, Ph.D.
Dentali Botanical Sciences

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February 25, 2021

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The use of this microorganism in the production of food products is historic. The application of the specific strain ***Bifidobacterium infantis* CBT BT1** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Cell Biotech Co. Ltd., a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Bifidobacterium infantis* CBT BT1** as an ingredient in dairy products is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Mary C. Mulry, Ph.D. (Foodwise), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. ***Bifidobacterium infantis* CBT BT1**, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products that include Cell Biotech Co. Ltd. ***Bifidobacterium infantis* CBT BT1** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good

Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on a combination of historic use of the microorganism in food products with support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY JEANNE MOLDENHAUER, M. SC.

I, Jeanne Moldenhauer, hereby affirm that ***Bifidobacterium infantis* CBT BT1** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: [redacted] Date: 6APR21

Jeanne Moldenhauer, M. Sc.
Excellent Pharma Consulting

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Cell Biotech Co. Ltd. *Bifidobacterium infantis* CBT BT1

February 25, 2021

Cell Biotech Co. Ltd. intends to market ***Bifidobacterium infantis* CBT BT1** as an ingredient in dairy products. ***Bifidobacterium infantis* CBT BT1** is produced by growth of a certified source strain of the organism in an appropriate medium. The strain is verified prior to inoculation of the medium. The resultant microorganism is freeze-dried for use in dairy products.

The use of this microorganism in the production of food products is historic. The application of the specific strain ***Bifidobacterium infantis* CBT BT1** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Cell Biotech Co. Ltd., a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Bifidobacterium infantis* CBT BT1** as an ingredient in dairy products is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Mary C. Mulry, Ph.D. CFS (FoodWise One LLC), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. ***Bifidobacterium infantis* CBT BT1**, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products that include Cell Biotech Co. Ltd. ***Bifidobacterium infantis* CBT BT1** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good

Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on a combination of historic use of the microorganism in food products with support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY MARY C. MULRY, PH.D. CFS

I, Mary Mulry, hereby affirm that ***Bifidobacterium infantis* CBT BT1** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: [redacted] Date: 3/18/21

Mary C. Mulry, Ph.D. CFS
FoodWise One LLC

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE (Subpart E of Part 170)

Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No._____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd):* 2021-12-06

4 For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd):* _____

SECTION B INFORMATION ABOUT THE NOTIFIER

1a. Notifier	Name of Contact Person Myung-jun Chung	Position or Title CEO		
	Organization *(if applicable)* Cell Biotech Co. Ltd.			
	Mailing Address *(number and street)* 50 Agibong-ro, 409 Beon-gil			
City Wolgot-myeon, Gimpo	State or Province Gyeonggi-do	Zip Code/Postal Code	Country Korea, Republic of	
Telephone Number +82 31 987 6205	Fax Number	E-Mail Address ceo@cellbiotech.com		
1b. Agent or Attorney *(if applicable)*	Name of Contact Person Jim Lassiter	Position or Title COO		
	Organization *(if applicable)* REJIMUS, INC.			
	Mailing Address *(number and street)* 600 W Santa Ana Blvd Suite 1100			
City Santa Ana	State or Province California	Zip Code/Postal Code 92701	Country United States of America	
Telephone Number 9492290072	Fax Number	E-Mail Address jim@rejimus.com		

SECTION C GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

Bifidobacterium infantis CBT BT1

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☒ Electronic files on physical media

☒ Paper

If applicable give number and type of physical media

1 DVD+R

3. For paper submissions only:

Number of volumes 1

Total number of pages 35

4. Does this submission incorporate any information in CFSAN's files? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for conclusions of GRAS status *(Check one)*

☒ Scientific procedures *(21 CFR 170.30(a) and (b))* ☐ Experience based on common use in food *(21 CFR 170.30(a) and (c))*

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

SECTION D INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

The intended use of Bifidobacterium infantis CBT BT1 is a food ingredient for inclusion in dairy products where standards of identity do not preclude such use. The intended addition level to these foods is up to 1 × 10^11 CFU per serving.

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☒ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☐ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E PARTS 2 7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete PART 1 is addressed in other sections of this form)

☒ PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).

☒ PART 3 of a GRAS notice: Dietary exposure (170.235).

☒ PART 4 of a GRAS notice: Self-limiting levels of use (170.240).

☒ PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).

☒ PART 6 of a GRAS notice: Narrative (170.250).

☒ PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

SECTION F SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that Cell Biotech Co. Ltd.
(name of notifier)

has concluded that the intended use*(s)* of Bifidobacterium infantis CBT BT1
(name of notified substance)

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. Cell Biotech Co. Ltd. agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so; agrees to send these data and information to FDA if FDA asks to do so.
(name of notifier)

50, Agibong-ro, 409 Beon-gil
(address of notifier or other location)

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
Jim Lassiter Digitally signed by Jim Lassiter Date: 2022.05.09 12:09:16 -07'00'	Jim Lassiter, President/COO	05/09/2022

SECTION G LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Form3667.pdf	Administrative
	GRASNotice_II964.1-CBI.1.4_Bifidobacterium_infantis_CBT_BT1_2022-05-09.pdf	Administrative
	Cell_Biotech_Co_Ltd_B_infantis_CBT_BT1_2018.pdf	GRAS Notice
	Bazanella_2017.pdf	GRAS Notice
	Candela_2007.pdf	GRAS Notice
	CDER_Starting_dose_in_Initial_Clinical_Trials_and_Therapeutics_in_Adult_Healthy_Volunteers_2005.pdf	GRAS Notice
	Del_Giudice_2017.pdf	GRAS Notice
	Dirar_1992.pdf	GRAS Notice
	Escribano_2018.pdf	GRAS Notice

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Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	EFSA_2012.pdf	GRAS Notice
	EFSA_Scientific_Opinion_on_the_Update_of_the_list_of_QPS-recommended_biological_agents.pdf	GRAS Notice
	Groeger_2013.pdf	GRAS Notice
	Health_Canada_Probiotics.pdf	GRAS Notice
	Hesseltine_1981.pdf	GRAS Notice
	Hill_2014.pdf	GRAS Notice
	Hod_2017.pdf	GRAS Notice
	Hod_2018.pdf	GRAS Notice
	Hoyos_1999.pdf	GRAS Notice

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Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Nout_1992.pdf	GRAS Notice
	Smilowitz_2017.pdf	GRAS Notice
	Steinkraus_1992.pdf	GRAS Notice
	Toure_2003.pdf	GRAS Notice
	Turroni_2014.pdf	GRAS Notice
	Ventura_2007.pdf	GRAS Notice
	Whorwell_2006.pdf	GRAS Notice